ADVANCE Design and Methodology
– Media Backgrounder –

ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) is the largest clinical trial ever performed in patients with type 2 diabetes.

Study rationale[1,2]

The ADVANCE study was set up to provide new evidence on the effects of more intensive blood pressure (BP) lowering and tighter glucose control on the risk of all complications in adults with type 2 diabetes. ADVANCE was intended primarily to evaluate the impact of each specific intervention, but the factorial design of the study also allows for assessment of the combined effects of tighter BP and glucose control together. The design of the trial is such that results will have direct clinical implications for the management of BP and glucose in a large proportion of all patients with type 2 diabetes.

Study objectives and design[1,2]

ADVANCE is an investigator-initiated and led, multicentre, randomised, placebo-controlled and 2x2 factorial study in type 2 diabetes. It was set up to determine the effect of Preterax (a BP lowering agent containing a fixed-dose combination of the ACE inhibitor perindopril and the diuretic indapamide) and an intensive glucose lowering intervention using Diamicron MR (a modified-release gliclazide-based therapy) on both macro vascular (stroke, MI, cardiovascular death) and micro vascular (new or worsening eye or kidney damage) events.

Study participants[1,2]

11,140 patients from 215 centres in 20 participating countries in Asia, Australasia, Europe and North America were recruited into ADVANCE. Approximately one third of patients came from Asian countries, with the remainder deriving predominately from Caucasian populations. Countries taking part in ADVANCE were highly reflective of the global type 2 diabetes problem. India, China, Russia and Germany all feature in the top 10 countries in the world in terms of number of people with diabetes – with China, the largest participating centre in ADVANCE, at position two on the global list.

ADVANCE participants were subject to key inclusion and exclusion criteria to ensure the recruitment of a wide cross-section of individuals with type 2 diabetes. Broadly speaking, any diabetic patient aged over 55 was eligible if at risk of vascular disease. In terms of baseline patient characteristics, 43% of participants were female, patients' mean age was 65.8 years, mean blood pressure was 145/81 mm Hg and average body mass index (BMI) was 28 kg/m^2. A total of 69% of study subjects had a history of hypertension, 75% were on current on BP-lowering therapy (most commonly an ACE inhibitor), 91% were receiving oral hypoglycaemic agents, 40% had a history of micro or macro vascular disease and 14% were smokers.

Study treatment[1,2]

Run-in period

Participants in ADVANCE were subject to a 6-week run-in period on open active blood pressure lowering treatment with Preterax and their usual glucose-lowering therapy. The run-in period was essential to assess the efficacy and safety of Preterax.

Randomisation

Assuming successful run-in over the first 6 weeks, patients were then randomised to one of the study's four treatment arms:

- Current cardiovascular therapy + Preterax (perindopril-indapamide combination) + intensive glucose control
- Current cardiovascular therapy + Preterax (perindopril-indapamide combination) + standard glucose control
- Current cardiovascular therapy + placebo + intensive glucose control
- Current cardiovascular therapy + placebo + standard glucose control

Randomisation followed ADVANCE's 2x2 factorial design and was stratified by study centre, history of macro vascular or serious micro vascular disease. Other classes of BP-lowering drugs could be prescribed at the discretion of the study clinicians.

Study drugs

- BP lowering comparison

For the first 3 months after randomisation, all patients received one tablet of Preterax (2.0 mg perindopril / 0.625 mg indapamide) per day or matching placebo. After 3 months, the daily dose was doubled (total dose 4.0 mg perinodpril / 1.25 mg indapamide). Treatment continued at this dose until the follow-up period of the study was completed.

- Glucose control comparison

For the glucose control element of ADVANCE, patients were assigned to either intensive glucose-lowering therapy, including a modified-release gliclazide-based glucose control (Diamicron MR), or to standard guidelines-based therapy. The intensive regimen targeted an HbA1c of 6.5% or less and so relied on maximisation of both drug therapy and non-drug interventions to achieve and maintain this tight control. Standard control simply involved the usual practice of the responsible physician following any relevant local, regional or national guidelines. The relevant glucose control measures used in each study arm were then maintained until the end of the ADVANCE follow-up period.

Study follow-up[1,2]

Patients in ADVANCE were to be followed-up for an average of 4.5 years, with a minimum follow-up period of 3 years and a maximum of 6 years. At all follow-up time points, blood pressure and HbA1c were measured. Patients were also assessed for the occurrence of study outcomes at every visit, with quantitative assessment of urinary protein and a formal eye examination at the 2nd and 4th years. In practice, as the events rates in ADVANCE proved less than planned, follow-up in the blood pressure lowering and glucose-control arms actually continued for longer than initially intended up to June 2007 (and anticipated up to December 2007) in order to ensure the planned levels of statistical power were maintained.

Study outcomes[1,2]

There were two primary outcomes for each randomised comparison in ADVANCE, to be analysed jointly and separately:

- *Major macro vascular complications* – the composite of non-fatal stroke, non-fatal acute coronary syndrome and death from any cardiovascular cause
- *Major micro vascular complications* – the composite of new or substantially worsening nephropathy (defined as development of macroalbuminuria, doubling of serum creatinine to ≥ 200 µmol/L, the need for dialysis or transplantation or death from renal disease) or micro vascular eye disease (defined as the need for retinal photocoagulation therapy, development of proliferative retinopathy, macular oedema or diabetes-related blindness)

Secondary outcomes included a broad range of cause-specific vascular and non-vascular events, cognitive function and dementia, health-related quality of life and cost-effectiveness.

ADVANCE substudies[1,2]

In addition to its primary aim, ADVANCE also included four major substudies looking at heart and eye function after intervention, cost-effectiveness and quality of life and genetic factors.

- *The ADVANCE Echocardiography Study* was set up to examine the effects of study treatments on heart function in around 500 patients.
- *The ADVANCE Retinopathy Measurements (AdRem) Study* was performed to examine the effects of study treatments on eye disease in around 2000 patients.
- *The ADVANCE Cost Effectiveness and Quality of Life Substudy Objectives (CEQoL)* was designed to investigate the cost effectiveness of the treatment regimens employed in ADVANCE and their impact on qualify of life.
- *Prognomix* was designed to identify the genotypic predictors of vascular complications, specifically heart attack, stroke and nephropathy, in type 2 diabetics.

– Ends –

References

[1]ADVANCE Collaborative Group (2001). "Rationale and design of the ADVANCE study: a randomised trial of blood pressure lowering and intensive glucose control in high risk individuals with type 2 diabetes." J Hypertens 19(Suppl 4): S21-28.

[2]ADVANCE Collaborative Group, A. Patel, et al. (2005). "ADVANCE - Action in Diabetes and Vascular Disease: patient recruitment and characteristics of the study population at baseline." Diabet Med 22: 882-8.

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[4]Chalmers J, editor. ADVANCE: New Approaches for the Prevention of Vascular Disease in Type 2 Diabetes. Issue 1. Wolters Kluwer Health; 2007.

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